REMARKS

Claims 29, 31, 33-36, 40-42, 45-48, 51-52, and 54, and 56 are pending. Claims 30, 32, 44, 49-50, 53, 55, and 57-58 were canceled, and claims 29, 31, 33, 34, 39-41, 45-47, and 54 were amended. The amendments to independent claims 29, 33, 34 are supported by disclosure at page 5, lines 14-16, of the specification. Claims 31, 39, and 45 were amended to add reference to an antibody-producing hybridoma cell line, which was deposited with the American Type Culture Collection (ATCC). The remaining claim amendments were made to correct typographical errors and claim dependency.

The specification has been amended to clarify that HAAH polypeptide refers to the amino acid sequence of SEQ ID NO:2 and HAAH cDNA refers to the nucleotide sequence of SEQ ID NO3. The claims have also been amended accordingly. The specification has also been amended to insert a reference to a sequence (SEQ ID NO:2) on page 6, line 16.

With respect to the Declaration/ Power of Attorney, co-inventor, Dr. Carlson, has initialed and dated the correction of his home address. An initialed/dated copy of the Combined Declaration and Power of Attorney document is submitted herewith.

No new matter has been added by this amendment.

35 U.S.C. § 112, second paragraph

Claims 29, 30, 33-36, 42, 43, 48, 51, 52, 56, and 57 were rejected for indefiniteness for recitation of "HAAH" as the only means of identifying a protein to which the claimed antibodies bind. As requested by the examiner, the claims have been amended to insert a sequence identifier.

35 U.S.C. § 112, first paragraph

Claims 31, 32, 39, 40, 41, 44-47, 50, 53-55, and 58 were rejected for lack of enablement.

Claim 32 has been canceled. The remaining claims have been amended to identify an antibody-producing hybridoma cell line, which was deposited with the ATCC. A copy of the ATCC deposit receipt is submitted herewith.

Claims 29, 30, 33-36, 42, 43, 48, 49, 51, 52, 56, and 57 were rejected for lack of written description. Claim 29 has been amended to require that the antibody bind to an epitope of within 650 to 700 of SEQ ID NO:2. In view of the amendment, this rejection can now be withdrawn.

Claims 33, and 45-52 were rejected for lack of enablement. Claim 33 has been amended to require a composition, which includes a monoclonal antibody that binds to an epitope within a catalytic domain of HAAH linked to a cytotoxic agent. In view of the present amendment, Applicant submits that this ground of rejection is moot.

35 U.S.C. § 102

Claims 29 and 43 were rejected for anticipation by Radosevich et al. as evidenced by Radosevich (USPN 6,166,176; "the 176 patent"). Claim 43 was canceled, and claim 29 was amended to require binding to an epitope within amino acids 650-700 of SEQ ID NO:2. Neither of the Radosevich references describe an antibody that binds to the required domain of HAAH (SEQ ID NO:2) now required by the claims.

Claims 29, 33, 43, and 49 were rejected for anticipation by Sinkule et al. as evidenced by Radosevich (the '176 patent) and the abstract of Tomida at al. The amended claims are novel over the cited art. Both Sinkule and Radosevich describe monoclonal antibody 44-3A6, which binds to residues 117-123 of labyrinthin (corresponding to residues 175-181 of HAAH). Claims 29 and 33 require that the claimed monoclonal antibody bind to an epitope within residues 650-

700 of SEQ ID NO:2, a domain that is not present in labyrinthin. Therefore, the amended claims are not anticipated by Sinkule et al.

Claims 29, 43, and 44 were rejected for anticipation by Lavaissiere et al. As was discussed above, claims 43 and 44 were canceled. Claim 29 was amended to require antibody binding to a specific epitope region of HAAH (residues 650-700 of SEQ ID NO:2). Such a binding specificity is not described by Lavaissiere et al. Therefore, this rejection should be withdrawn.

Claims 29 and 42 were rejected for anticipation by Carter et al. Amended claim 29 recites a monoclonal antibody that binds to an epitope within carboxy-terminal residues 650-700 of SEQ ID NO:2, whereas the antibodies of Carter bind to sequences, which may correspond to certain amino-terminal sequences of SEQ ID NO:2. The amended claims are therefore novel over Carter et al.

Applicants submit that the claims as now amended are not anticipated by the cited art and respectfully request withdrawal of the rejections for anticipation.

35 U.S.C. § 103

Claims 29, 34-36, 42, 43, 56, and 57 were rejected for obviousness over Radosevich et al. as evidenced by the '176 patent in view of Wels et al. and Schlom et al. The amended claims are nonobvious over the cited art, because neither of the Radosevich prior art references describe an antibody that binds to residues 650-700 of SEQ ID NO:2. The binding specificity is not provided by any of the secondary references, i.e., the Wels and Schlom references also fail to describe the HAAH domain now required by the amended claims. Therefore, this combination of references does not suggest the claimed invention.

Claims 29, 33, 42, 43, 48, and 49 were rejected for obviousness over Sinkule et al. as evidenced by the '176 patent and the abstract of Tomida et al. for the reasons set forth in the Examiner's rejection for anticipation by Sinkule et al. (section 14 of the Office Action). Sinkule et al. describe a specific monoclonal antibody, which binds to an epitope far removed from residues 650-700 of SEQ ID NO:2. Neither Sinkule et al. nor the '176 patent describe an epitope or HAAH domain defined by the amended claims. Tomida et al. describe drug resistance in tumor cells and also fail to provide any sequence information lacking in Sinkule. In view of the amendment of claim 29 (requiring that the antibody bind to an epitope within residues 650-700 of SEQ ID NO:2), Applicants submit that the amended claims are non-obvious over the cited combination of references.

Claims 29, 30, 43, and 44 were rejected for obviousness over Lavaissiere et al. in view of Goding and the '176 patent. The Examiner states:

> One of skill in the art would have been motivated to make a specific antibody which would bind to the carboxyl terminus of HAAH to avoid cross reactivity to Labyrinthin, and attain an accurate measurement of the amount of HAAH protein in a sample, as levels of Labyrinthin would not be correlated with hydroxylation.

Lavaissiere et al. fail to describe or suggest the specific region (residues 650-700 of SEQ ID NO:2) required by the amended claims. The '176 patent fails to describe such a sequence, because the protein described by the '176 patent is a splice variant that lacks a sequence defined by residues 650-700 of SEQ ID NO:2. Goding is a general reference from nearly twenty years ago, which describes the advantages of monoclonal antibodies compared to antisera. This combination in no way suggests a monoclonal antibody with the precise binding specificity required by the amended claims. Moreover, neither reference makes any mention at all of a

reason or need to distinguish HAAH from Labyrinthin; therefore, there is no motivation to make the antibody now defined by the amended claims.

Double Patenting

Claims 29, 31, 39, 43, 44 and 34, 57, and 58 were provisionally rejected for obviousness-type double patenting over claims 35 and 39-43 of copending application USSN 09/859,604 (the '604 application) in view of Lavaissiere et al. The '604 application is a continuation-in-part of the present application. Neither the cited claims of the '604 application nor Lavaissiere describe the an antibody that binds to residues 650-700 of SEQ ID NO:2; therefore, the rejection of claims 29 and 34 should be withdrawn. With respect to claims 31 and 39, Applicants will file a terminal disclaimer (if still applicable), upon notification of allowable claims.

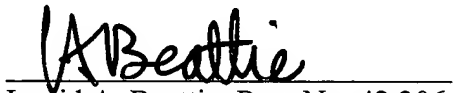
Claims 29, 31, 34-36, 39-44 and 53-58 were rejected for obviousness-type double patenting over claims 35 and 39-43 of the '604 application in view of Lavaissiere et al. and Schlom. As was discussed above, neither the claims of the '604 application nor the cited literature describe or suggest the binding specificity now required by claims 29 and 34 (and those claims depending therefrom). With respect to the remaining claims, a terminal disclaimer (if still applicable) will be filed upon notification of allowable claims in the present application.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance.

Applicants file concurrently herewith a petition for a two (3) month extension of time, together with a check for $930.00 to cover the fee pursuant to 37 C.F.R. § 1.17(a)(3). With the extension, this amendment is due on or before April 28, 2003. The Commissioner is hereby authorized to charge same, or credit any overpayment, to Deposit Account No. 50-0311 (Reference No. 21486-032 DIV5).

Respectfully submitted,



Ingrid A. Beattie, Reg. No. 42,306
Attorney for Applicant
c/o MINTZ LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel.: (617) 542 6000
Fax: (617) 542-2241

EXHIBIT A

Marked up Version

In the specification:

On page 1, replace paragraph on lines 19-35 with the following paragraph.

The invention features a method for diagnosing a malignant neoplasm in a mammal by contacting a bodily fluid from the mammal with an antibody which binds to an human aspartyl (asparaginyl) beta-hydroxylase (HAAH) polypeptide under conditions sufficient to form an antigen-antibody complex and detecting the antigen-antibody complex (for the purposes of this specification, HAAH polypeptide refers to the amino acid sequence of SEQ ID NO:2 and HAAH cDNA refers to the nucleotide sequence of SEQ ID NO:3). Malignant neoplasms detected in this manner include those derived from endodermal tissue, e.g., colon cancer, breast cancer, pancreatic cancer, liver cancer, and cancer of the bile ducts. Neoplasms of the central nervous system (CNS) such as primary malignant CNS neoplasms of both neuronal and glial cell origin and metastatic CNS neoplasms are also detected. Patient derived tissue samples, e.g., biopsies of solid tumors, as well as bodily fluids such as a CNS-derived bodily fluid, blood, serum, urine, saliva, sputum, lung effusion, and ascites fluid, are contacted with an HAAH-specific antibody.

On page 6, replace paragraph on lines 5-16 with the following amended paragraph.

For example, a compound which inhibits HAAH hydroxylation is a polypeptide that binds a HAAH ligand but does not transduce an intracellular signal or an polypeptide which

contains a mutation in the catalytic site of HAAH. Such a polypeptide contains an amino acid sequence that is at least 50% identical to a naturally-occurring HAAH amino acid sequence or a fragment thereof and which has the ability to inhibit HAAH hydroxylation of substrates containing an EGF-like repeat sequence. More preferably, the polypeptide contains an amino acid sequence that is at least 75%, more preferably at least 85%, more preferably at least 95% identical to SEQ ID NO:2.

On page 17, after line 22, insert the following new paragraph.

--Deposit of Biological Materials

Under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure, hybridoma FB501 (which produces monoclonal antibody FB50; designated ATCC accession no. PTA 3386), hybridoma HA386A (which produces monoclonal antibody 86A; designated ATCC accession no. 3385), hybridoma HA15C7A (which produces monoclonal antibody 5C7; designated ATCC accession no. 3383), and hybridoma HA219B (which produces monoclonal antibody 19B; designated ATCC accession no. 3384) were deposited on May 17, 2001, with the American Type Culture Collection (ATCC) of 10801 University Boulevard, Manassas, Va. 20110-2209 USA..

Applicants' assignee represents that the ATCC is a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. All restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent. The material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122. The deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing

of a sample of the deposited plasmid, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. Applicant's assignee acknowledges its duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.--

On page 47, lines 1-12, replace Table 4 with the following amended Table.

Table 4: Overexpression of enzymatically active HAAH indicates malignancy

Cdna	# of foci ± S.D.[b]	NIH 3T3 clone	# of colonies[e]
pcDNA3 (mock)	6.0 ± 3.3	pcDNA (mock)	0.4 ± 0.5
murine [H]AAH	14.0 ± 2.9	clone 18[d]	6.2 ± 2.9
mutant murine [H]AAH[a]	1.6 ± 1.0	clone 16[e]	4.7 ± 6.5
[human] HAAH	32.0 ± 5.4		
v-scr	98.0 ± 7.1		

a. enzymatically inactive [H]AAH
b. P<0.01 compared to mock and mutant murine [H]AAH
c. P<0.001 compared to mock
d. Clone 18 is a stable cloned NIH 3T3 cell line that overexpression human HAAH by approximately two fold.
e. Clone 16 is a stable cloned NIH 3T3 cell line that overexpresses human HAAH by about 50%.

In the claims:

Cancel claims 30, 32, 44, 49-50, 53, 55, and 57-58. Amend claims 29, 31, 33, 34, 39-41, 45-47, and 54.

29. (amended) A monoclonal antibody that binds to an epitope within a catalytic domain of HAAH, said domain comprising residues 650-700 of SEQ ID NO:2.

31. (amended) [The antibody of claim 29] A monoclonal antibody that binds to an epitope of SEQ ID NO:2, wherein said monoclonal antibody is selected from the group consisting of 5C7 produced by hybridoma ATCC designation PTA 3383, [5E9,] 19B produced by hybridoma ATCC designation 3384, [48A, 74A, 78A,] and 86A produced by hybridoma ATCC designation 3385.

35. (amended) A composition comprising a monoclonal antibody that binds to an epitope within a catalytic domain of HAAH, said antibody being linked to a cytotoxic agent, wherein said [composition preferentially kills tumor cells compared to non-tumor cells] domain comprises residues 650-700 of SEQ ID NO:2.

36. (amended) A kit for diagnosis of a tumor in a mammal, comprising a monoclonal antibody that binds to an epitope within a catalytic domain of HAAH, said catalytic domain comprising residues 650-700 of SEQ ID NO:2.

40. (amended) [The antibody of claim 29] A fragment of a monoclonal antibody that binds to an epitope of SEQ ID NO:2, wherein said antibody is a [HAAH-binding fragment of FB50] is produced by hybridoma ATCC designation PTA 3386.

40. (amended) The antibody of claim 39, wherein said fragment is a [FB50] Fab or (Fab)2 fragment.

41. (amended) The antibody of claim 39, wherein said antibody is a [FB50] single chain Fv molecule.

45. (amended) [The] A composition [of claim 33] comprising [, wherein said antibody is a HAAH-binding] a fragment of [FB50] an antibody produced by hybridoma ATCC designation PTA3386, said fragment being linked to a cytotoxic agent.

46. (amended) The composition of claim [33] 45, wherein said [antibody] fragment is a [FB50] Fab or (Fab)2 fragment.

47. (amended) The composition of claim [33] 45, wherein said [antibody is a FB50] fragment is a single chain Fv molecule.

52. (amended) The composition of claim 33, wherein said cytotoxic agent is [diptheria] diphtheria toxin.

54. (amended) The kit of claim 34, wherein said antibody is a [FB50] Fab or (Fab)2 fragment.

55. (amended) The kit of claim 34, wherein said antibody is a [FB50] single chain Fv molecule.